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(54) Title: *IN SITU*-GENERATED SOLID RADIATION SOURCE BASED ON TUNGSTEN^{188}/RHENIUM^{188} AND THE USE THEREOF

(57) Abstract

A radiotherapeutical source of Rhenium^{188} comprising metallic Tungsten^{188} or a metal oxide of Tungsten^{188}.

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IN SITU - GENERATED SOLID RADIATION SOURCE BASED ON TUNGSTEN^{188} / RHENIUM^{188} AND THE USE THEREOF

Field of the Invention

The present invention relates to therapeutic radioactive sources, particularly radioactive sources utilizing Rhenium^{188} as a therapeutic agent. More particularly, the invention relates to novel therapeutic devices employing a radioactive source generated *in situ*.

Background of the Invention

The use of radiotherapy is quite common in modern medicine. Radiotherapy is used for a variety of uses, such as for post-surgery treatment of tumors, for various types of cancer therapy and, lately, the art has found that radiotherapy can be useful in preventing restenosis in patients treated for coronary diseases. Restenosis has been treated so far by short-term irradiation with radioactive sources located in catheters and wires, and by long-term irradiation with implanted devices, such as stents.

Many different radioactive materials have been used, including β- and γ-emitters. In typical devices employed in the art, a radioactive portion is provided in a device to be inserted in a body cavity, in a variety of ways. In

one method the radioactive material is generated separately from the device, and attached thereto in a variety of ways, such as by containerization, coating, etc., and in other methods the device, e.g., a catheter, is irradiated shortly before use, to generate the radioactive material to be used for the treatment, and the device is then inserted into the body cavity.

The production of Rhenium^{188} (Re^{188}) from Tungsten^{188} (W^{188}) for pharmaceutical uses is described e.g. in US 5,382,388, US 5,186,913, US 5,145,636 and US 4,778,672. According to the prior art Re^{188} is generated in aqueous solution, and it must then be separated from the reagent, W^{188}, and complexed to organic and biological complexes prior to its injection into the body.

Another method of producing Re^{188} is via the neutron activation of Re^{187}. However, purified Re^{188} has a half life of about 17 hours, which is a very low shelf life for medical purposes. This means that, according to the prior art, in order to be able to use Re^{188} in therapy, irradiation of the device must take place shortly before the surgical procedure takes place, which requires suitable and complex logistics for the hospital.

The present invention exploits the production of W^{188} and its decay to Re^{188}, which are as follows:

Production: $W^{186} \xrightarrow{n,\ gamma} W^{187} \xrightarrow{n,\ gamma} W^{188}$

Decay: $W^{188} \xrightarrow{beta} Re^{188} \xrightarrow{beta} Os^{188}$

The half-life time ($t_{1/2}$) of W^{188} is 69 days and Os^{188} is stable. W^{188} is prepared by a double neutron activation of W^{186} target. The W^{186} target is made either from enriched W^{186} or from natural tungsten which has an abudance of 28.6% W^{186} ("Table of Isotopes", Lederer, Hollander and Perlman, John Wiley & Sons.)

The advantages of using β-emitting sources are known in the art, Particularly, β-emitting sources have a limited depth of penetration in tissue and are therefore particularly suited for treatments, such as the prevention of restenosis, which do not require in-depth penetration and in which, in fact, in-depth penetration is undesirable. The β-emission of R^{188} is suitable for penetration depth of 4-5 mm in tissue, and the γ photons emission can be used to image the source within the body cavity. Furthermore, tungsten and rhenium have been used in medicine according to the known art, and no undesirable toxic effects have been disclosed to date (for toxicity see "The Merck Index", 1968, 8th Ed., p.916).

Another important advantage of tungsten and rhenium is their high atomic number, which makes them excellent x-ray radio opaque markers. This feature is important for catheterization procedures and, even more, for

non-opaque stents positioning within a vessel. Furthermore, in case of break or leak of part of the source, this x-ray contrast property enables the clinician to monitor its location and to attempt to retrieve it.

So far, however, the art has failed to provide a radioactive source which is convenient to use, which does not require expensive and hazardous irradiation procedures on the spot, and which provide the desired major proportion of β-emission, with only minor amount of γ-emission. Furthermore, the art has so far failed to provide such a source which, in addition to the abovementioned desirable properties, is also relatively long-lived.

It is an object of the present invention to provide a radioactive source for therapy, which overcomes the abovementioned drawbacks of prior art sources.

It is a further object of the invention to provide medical devices utilizing the source of the invention, which can be utilized in a variety of radiotherapy procedures, and particularly for the treatment and/or the prevention of restenosis.

It is another object of the present invention to provide a long life Re^{188} radioactive therapeutic device.

It is yet another object of the present invention to provide a method for the manufacture of a Re^{188} radioactive therapeutic device that is free from the need to purify and to complex Re^{188} prior to use.

Other objects and advantages of the invention will become apparent as the description proceeds.

Summary of the Invention

According to the present invention, W^{188} is used in *in vivo* generation of Re^{188} for the purpose of radioactive therapy.

Thus, the present invention provides a therapeutic device comprising a source wire having a W^{188}/Re^{188} source at its distal tip.

Preferably, said source wire is in the form of any of the group which consists of, but not limited to, catheter, guidewire, stent or implant (pellet).

Optionally, said source wire is made of tungsten or made of other applicable matter and coated by tungsten.

Preferably, the physical form of said source is selected from the group which consists of, but not limited to, wire, coil, spring, seeds, powder or pellets encapsulated in a thin outer shell.

Preferably, the chemical form of said source is selected from the group which consists of, but not limited to, tungsten metal or tungsten trioxide.

Preferably, the length of said source is between 1 - 50 mm, more preferably between 5 - 35mm, and its diameter is between 0.2 - 10 mm, more preferably between 0.34 - 5mm.

More preferably, when utilized in high radiation catheters said source is 25 - 35mm long, its diameter being between 0.34 - 1.1mm; when utilized in stents, the source is 10 - 30 mm long, with a diameter of 0.7 - 3 mm, when utilized as interstitial implants the source is about 3 - 10 mm long with a diameter of about 0.3 - 1 mm, and when utilized as a round shape source, its diameter is about 3 - 7 mm. A "high radiation source" is defined as a source that can irradiate the target organ and achieve the desired dose in several minutes. Illustrative and non-limitative examples of suitable doses are those comprised between 1,500 - 5,000 rad; the activity is typically up to 100 mC, W^{188}, and the irradiation time is up to up to 30 minutes.

Preferably, The W/Re source is within the activity range of 0.25 microcuries to 100 millicuries of W^{188}.

Brief Description of The Drawings

In the drawings:

Fig. 1 schematically illustrates the positioning of a radioactive source on a catheter;

Fig. 2 shows a stent made of metal wire and provided with a plurality of implanted radioactive elements;

Fig. 3 schematically illustrates an implant according to one preferred embodiment of the invention; and

Fig. 4 schematically illustrate applicators of radioactive sources which are particularly suitable for eye therapy.

Detailed Description of the invention

In one aspect, the invention is directed to a radiotherapeutical source of $Rhenium^{188}$ comprising metallic $Tungsten^{188}$ or a metal oxide of $Tungsten^{188}$. Thus, the invention provides for the first time a means to generate β-radiation from a $Rhenium^{188}$ source, for an extended period of time, at a constantly predictable rate, from a pre-irradiated Tungsten source. Apart from the aforementioned advantage of excellent logistic for the hospital, the catheter of the invention, comprising the W/Re irradiation system, has the

added advantage of being reusable, so that the same catheter can be transferred from one patient to the other, of course after suitable washing and sterilization procedures.

In another aspect, the invention is directed to therapeutic device comprising a radioactive source for the *in situ* generation of Rhenium^{188} from Tungsten^{188}.

Many different therapeutic devices can be made according to the invention. Illustrative and non-limitative examples of useful devices include catheters, guidewires, stents and implants.

According to a preferred embodiment of the invention the therapeutic device comprises a main body at least a portion of which consists of, or is coated with, or houses, a radioactive source for the *in situ* generation of Rhenium^{188} from Tungsten^{188}. The irradiation of the W source for a catheter is carried out as follows: the W coil is loaded in a quartz capsule, typical dimensions being 9 mm diameter and 45 mm length, or alternatively in aluminum cans, typical dimensions being: diameter: 23 mm; length: 70 mm. The cans are positioned in the reactor core and irradiated. Homogeneity of the flux is obtained by rotating the sample during irradiation.

The decay of the source activity with time is illustrated in Tables I and II:

Table I

Source Activity Decay with Time - W^{188}

Time (days) after irradiation	% of original activity
0	100
69	50
138	25

Table II

Source Activity Decay with Time - Re^{188}

Time (days) after irradiation	% of original activity
0	100
17	50
34	25
51	12.5

From the above tables it can be seen that in the W^{188}-Re^{188} system the time is dominated by W^{188}.

According to a preferred embodiment of the invention there is provided a therapeutic device wherein the radioactive source is located at its distal end. Such devices can be made of a variety of materials, as will be appreciated by persons skilled in the art. A preferred construction for the therapeutic device is that in which the main body is made of, or coated with, tungsten. However, it should be understood that the invention is by no means limited to any particular construction material or combination of materials for the

therapeutic device. Preferably, the tungsten is in metallic or tungsten trioxide form.

According to a preferred embodiment of the invention the *in situ*-generated source of Rhenium^{188} is in the form of a device selected from among wires, coils, springs, seeds, powders or pellets encapsulated in an outer shell.

In one example of therapeutic device the length of the source is between about 5 mm and 35 mm. When the therapeutic device of the invention is a catheter, it may typically have a length of between about 25mm and 35mm, and a diameter of between 0.34 mm to 1 mm. When the therapeutic device of the invention is a stent, it may typically have a length of between about 10 mm and 30 mm, and a diameter of between about 0.7 mm and 3 mm.

When the therapeutic device of the invention is an interstitial implant, it may typically have a length of about 5 mm and a diameter of about 0.4 - 1 mm. When the therapeutic device according to the invention is a round shaped source it may typically have a diameter of about 3 - 7 mm.

The activity of the source may change according to the specific use for which it is designed. Illustrative and non-limitative therapeutic devices may comprise a source having an activity of between 0.25 microcuries to 100 millicuries of W^{188}.

The invention also encompasses the use of Tungsten^{188} as a precursor for the *in situ* generation of therapeutically active Rhenium^{188}.

As stated, the source wire (or other device) is made of tungsten or of any other suitable material which is coated with tungsten. Said wire is cleaned by means e.g. of washing and heat-sterilization. The wire is then irradiated, in order to produce a radioactive source wire. In many cases, the source wire is not utilized immediately after its irradiation, in order to allow short-lived isotopes, which may be undesirable in therapy, to decay.

In case that the source wire is in the form of a catheter, the radioactive wire source segment can be mounted on a catheter in a hot cell and be sealed, e.g., by a heat-shrinkable polymer.

In case that the source wire is in the form of a stent, known stents such as a titanium or nitinol stent can be coated with tungsten for the purposes of the present invention, or specifically manufactured stents can be provided, using tungsten as a construction material. In the first case, about 1 - 10 micrograms of W^{186} or natural W should be implanted at about 0.2μm depth in the stent surface, so that leaking of radioactivity is minimized and the β-radiation is not absorbed. The required activity range in a stent is between 0.24 and 40 microcuries.

The high activity level catheter sources are useful in one-time short irradiation time treatments, such as in preventing the restenosis in coronary arteries (PTCA), or for eye treatments. The acceptable dose for this purpose is 18-25Gy. This dose can typically be achieved in 5 - 15 minutes of irradiation.

It should be noted that the β-emission provided by the W^{188} is completely blocked in the medium between the source surface and the vessel wall, and does not have significant radiobiological effect. One of the advantages of using titanium source wire is that titanium is not significantly activated by the irradiation process. The maximal energy of W^{188} is 0.35 MeV. This is β-irradiation and calculations show that electrons of this energy can travel in water for a maximal distance of 1 mm, which insures that the energy of W^{188} itself cannot reach the blood vessel and cannot contribute significantly to the dose to the wall.

The present invention is especially useful in applications with required depth of penetration of 4-5mm with a minimal damage to healthy tissues. This result cannot be achieved using some of the γ and x-ray sources acceptable in therapy.

The use of W^{188} is convenient and flexible rendering it attractive for use in hospitals. W^{188} can be produced in common medium flux reactors without the need for cyclotrons as in the case of P-32 and V-48 implanted stents.

As will be appreciated by the skilled person, the use of radiotherapy in general, and the use of β-radiation in particular, are well known in the art. Furthermore, the use of radiotherapy for the purposes to which the present invention is directed is also well known. Therefore, no detailed discussion of medical and therapeutic aspects is made herein, for the sake of brevity, and the reader is referred to the many publications dealing with the medical aspects of, e.g., restenosis and its prevention by radiotherapy, such as V.J. Lewington, *Eu. J. Nuc. Med.* 20, 66-74 (1993), "Targeted Radionuclide Therapy for Bone Metastases"; or M. Chinol et al., *J. Nuc. Med.* 34, 1536-1542 (1993), "Chemistry and Biological Behaviour of Sm-153 and Re-186 Labeled Hydroxyapatite Particles".

A major problem of extensive leakage (5-25%) was registered when using radionuclides as a Re^{186}, Sr^{89} and others for radiation synovectomy. According to the present invention a solid source of W/Re will be on the one hand effective in treating the synovial joint and on the other hand will exhibit minimal extra-articular leakage of radioactivity.

Fig. 1 schematically illustrates the positioning of a radioactive source on a catheter. Fig. 1A shows a catheter, generally indicated by numeral 1, which is shown truncated at extremity 2. The catheter is provided at its distal end 3 (shown in cross-section along the axis of the catheter) with a tungsten coil 4 (also shown separately in Fig. 1B), which is the radioactive source. The coil 4 is coiled around elongated portion 5 of catheter 1, and is covered by an external sheath 6, which may be of any suitable material, e.g., plastic or metal.

Fig. 2 shows a stent 7, made of metal wire and provided with a plurality of implanted radioactive elements, 8, three of them being indicated in the figure.

Fig. 3 schematically illustrates an implant according to one preferred embodiment of the invention. Implant 9, which in this particular example has a cylindrical form, consists of a tube 10, which may be of any suitable material, which tube houses a plurality of pellets 11. The tube and the pellets of Fig. 3 are shown in longitudinal cross-section. Each pellet 11 consists of an outer shell 12, which is typically made of titanium, and of a radioactive W^{188}/Re^{188} core 13.

Fig. 4 schematically illustrate applicators of radioactive sources which are particularly suitable for eye therapy, Fig. 4A showing a round shaped

applicator, and Fig. 4B a rod-shaped one. The applicator, 14, simply consists of a handle 15 at the end of which there is provided a radioactive source 16, in any suitable shape, e.g., round or rod-like.

The above and other characteristics and advantages of the invention will become apparent through the following illustrative and non-limitative examples of preparation.

Example 1

Natural tungsten W^{186} coil was prepared from a tungsten wire having a purity of 99.95%, and a diameter of 0.13-0.2mm. The coil was about 30mm long and had an outer diameter of about 1mm, and weighed about 225mg. The coil was washed with water and alcohol in an ultrasonic bath in order to remove impurities. After the wash the coil was heated in vacuum to 1000°C for 20 hours. The coil was then kept in a sealed container until used.

Example 2

A coil prepared according to Example 1 is neutron irradiated in a high flux reactor for about 20 days with thermal neutron flux of about $1.5 \cdot 10^{15}$ neutrons/cm^2•sec to produce about 100 millicuries of W^{188}/Re^{188}. The coil is not used for 1 week subsequent to its irradiation, in order to allow short-lived isotopes to decay. The dosimetry is determined by a Ge spectrometer and a Capintek dose calibrator.

Example 3

An irradiated coil (source) of Example 1 is mounted on a 142 cm polyimide or Ni/Ti catheter, on its distal end, and sealed with a heat shrink polymer.

Example 4

A 30 mm long support titanium or Ni/Ti guidewire, having a diameter of 0.36 mm is homogeneously electroplated with 60 mg of enriched W^{186} with a purity of 97.7%, or with 210 mg of natural W. The coated wire is treated and irradiated as in Examples 1 and 2. The 30 mm source is linked to a 112 mm Ti or Ni/Ti guidewire having a diameter of 0.36 mm (0.014"), by thrusting or screwing or welding.

Example 5

A 142 mm long titanium or Ni/Ti wire having a diameter of 0.36 mm (0.014") is electroplated at its distal 30 mm end with W186, as in Example 4.

Example 6

A 30 mm long support titanium or Ni/Ti wire (guidewire) having a diameter of 1 mm (0.039") is electroplated as in Example 4.

Example 7

A 142 mm long titanium or Ni/Ti wire, having a diameter of 1 mm (0.039") is electroplated as in Example 4 and treated and irradiated as in Examples 1 and 2.

Example 8

A titanium or nitrinol stent is electroplated as in Example 3 and treated and irradiated as in Examples 1 and 2.

The above description and examples have been provided for illustrative purposes only, and are not intended to limit the invention in any way. As will be apparent to the skilled person, many modifications, variations and adaptations may be made to the invention by persons skilled in the art, without departing from the spirit of the invention or exceeding the scope of the claims.

Claims

1. A radiotherapeutical source of Rhenium^{188} comprising metallic Tungsten^{188} or a metal oxide of Tungsten^{188}.

2. A therapeutic device comprising a radioactive source for the *in situ* generation of Rhenium^{188} from Tungsten^{188}.

3. A therapeutic device according to claim 2, which is a device selected from catheters, guidewires, stents and implants.

4. A therapeutic device according to claim 2 or 3 comprising a main body at least a portion of which consists of, or is coated with, or houses, a radioactive source for the *in situ* generation of Rhenium^{188} from Tungsten^{188}.

5. A therapeutic device according to claim 4, wherein the radioactive source is located at its distal end.

6. A therapeutic device according to claim 4 or 5, wherein the main body is made of, or coated or implanted with, tungsten.

7. A therapeutic device according to any of claims 2 to 6 wherein the *in situ*-generated source of Rhenium^{188} is in the form of a device selected

from among wires, coils, springs, seeds, powders or pellets encapsulated in an outer shell.

8. A therapeutic device according to any of claims 2 to 7 wherein the tungsten is in metallic or tungsten trioxide form.

9. A therapeutic device according to any of claims 2 to 8 wherein the length of the source is between about 5 mm and 35 mm.

10. A therapeutic device according to any of claims 2 to 9 which is a catheter, having a radioactive source at its distal end, said source having a length of between about 25 mm and 35 mm, and a diameter of between 0.34 mm to 1 mm.

11. A therapeutic device according to any of claims 2 to 9 which is a stent, having a length of between about 10 mm and 30 mm, and a diameter of between about 0.7 mm and 3 mm.

12. A therapeutic device according to any of claims 2 to 9 which is an interstitial implant, having a length of about 3 - 10 mm and a diameter of about 0.3 - 1 mm.

13. A therapeutic device according to any of claims 2 to 9, which is a round shaped source having a diameter of about 3 - 10 mm.

14. A therapeutic device according to any of claims 1 to 13, comprising a source having an activity of between 0.25 microcuries to 100 millicuries W^{188}/Re^{188}.

15. Use of $Tungsten^{188}$ as a precursor for the *in situ* generation of therapeutically active $Rhenium^{188}$.

16. A therapeutic device, essentially as described and illustrated.

17. Use of a $Tungsten^{188}/Rhenium^{188}$ radioactive source, substantially as described and with particular reference to the examples.

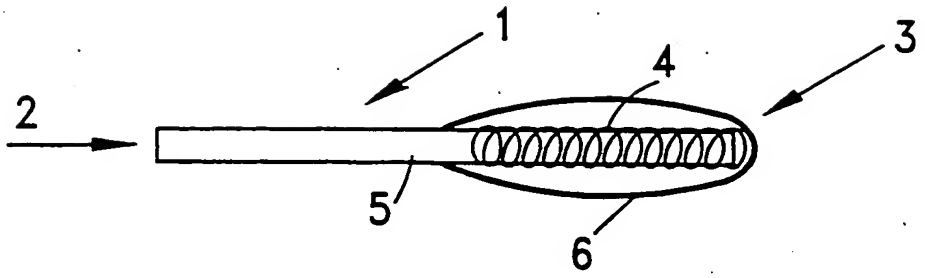

Fig. 1A

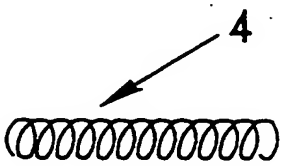

Fig. 1B

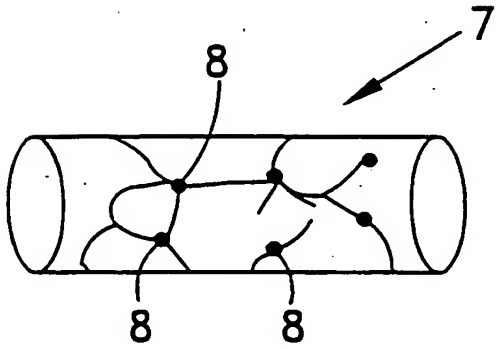

Fig. 2

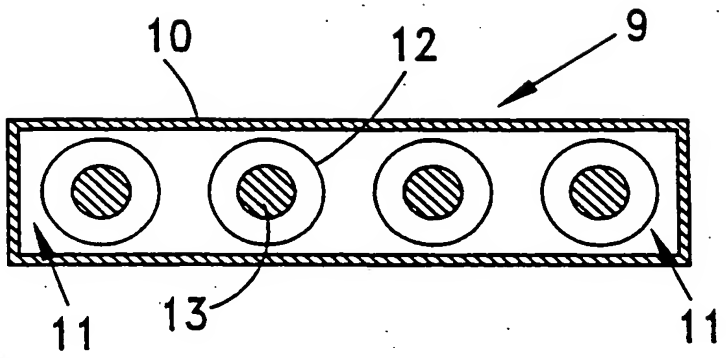

Fig. 3

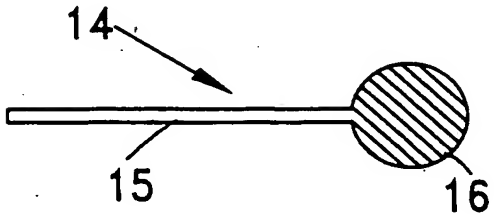

Fig. 4A

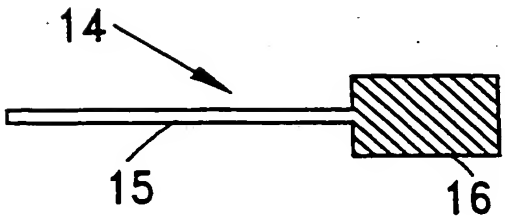

Fig. 4B

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61N 5/00
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 600/001-008

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,145,636 A (VANDERHEVDEN et al) 08 September 1992, entire document.	1, 2, 15-17 --- 3-14
X --- Y	US 5,186,913 A (KNAPP, JR. et al) 16 February 1993, entire document.	1, 2, 15-17 --- 3-14
A	US 5,674,177 A (HEHRLEIN et al) 07 October 1997, entire document.	1-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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